PATENT
Attorney Dock t No. 4249.0002-05

APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	
John B. SULLIVAN et al.	
Serial No. 08/405,454	Group Art Unit: 1644
Filed: March 15, 1995	Examiner: Ron Schwadron, Ph.D.
For: ANTIVENOM COMPOSITION CONTAINING FAB FRAGMENTS (As Amended)	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

APPELLANTS' BRIEF IN SUPPORT OF APPEAL UNDER 37 C.F.R. § 1.192

Pursuant to 37 C.F.R. § 1.192, Appellants submit this Appeal Brief in triplicate, along with the requisite fee pursuant to 37 C.F.R. § 1.17(c), to the Board of Patent Appeals and Interferences in support of their Appeal from the Final Office Action dated April 14, 1998 (Paper No. 33). Appellants initiated this Appeal from the final rejection of claims 40-42 and 45-47 by filing a Notice of Appeal on July 14, 1998, along with the fee required by 37 C.F.R. § 1.17(b). As an Appeal Brief, thus, became due on September 14, 1998, Appellants file herewith a Petition for a Five-Month Extension of Time, together with a check covering the requisite fee

This application is a continuation of application Serial No. 08/277,288, filed July 22, 1994, which is a continuation of application Serial No. 07/124,438, filed

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September 22, 1993, which is a continuation of application Serial No. 07/593,271, filed October 1, 1990, which is a division of application Serial No. 07/378,925, filed July 12, 1989, which is a division of application Serial No. 06/659,629, filed October 9, 1984, now U.S. Patent No. 4,849,352, issued July 18, 1989.

I. Real Party in Interest

The real party in interest in the pending appeal is the Assignee, Therapeutic Antibodies, Inc. of Nashville, Tennessee, by virtue of an assignment from Appellants, duly recorded.

II. Related Appeals and Interferences

Appellants, the undersigned, and the assignee know of no other appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in this Appeal.

III. Status of Claims

Appendix I contains the pending claims on appeal (40-42 and 45-47).

Applicants filed parent application Serial No. 07/124,438 with claims 1-30 and canceled claims 1-16 in the papers filing divisional application Serial No. 07/378,925. Appellants then filed the Preliminary Amendment of October 1, 1990, in divisional application Serial No. 07/593,271, canceling claims 17-19 and amending claims 20-26. Appellants then filed a Preliminary Amendment in application Serial No. 08/124,438 on

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December 16, 1993; amending claims 27, 29, and 30; canceling claims 20-26 and 28, and adding claims 31-39, resulting in claims 27 and 29-39 being pending.

Appellants amended claims 27 and 29 and canceled claims 30-36 in the Amendment of January 17, 1995, in application Serial No. 08/277,288 resulting in claims 27, 29, and 37-39 being pending. Appellants amended claims 27 and 29 in the Preliminary Amendment of October 5, 1995. Appellants then canceled claims 27, 29, and 37-39 and added new claims 40-49 in the Amendment of April 30, 1996, resulting in claims 40-49 being pending.

Appellants proposed amending claims 40-49 in the Amendment under 37 C.F.R. § 1.116 of January 27, 1997, but the Examiner did not enter the Amendment in the Advisory Action of February 12, 1997. Appellants amended claims 40-49 in the Amendment under 37 C.F.R. § 1.129(a) of April 15 1997.

Appellants canceled claims 43-44 and 48-49 and amended claims 40-45 in the Amendment of December 19, 1997, resulting in claims 40-42 and 45-47. Finally, Appellants proposed amending claims 41-42 in the Supplemental Amendment under 37 C.F.R. § 1.116 of August 5, 1997. The Examiner indicated that this Amendment would be entered upon the filing of an Appeal Brief in the Advisory Action of August 31, 1998 (Paper No. 40). Accordingly, claims 40-42 and 45-47 as Appellants reproduce in Appendix I, are pending in this application.

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IV. Status of Amendments

Other than the amendments Appellants proposed in the Amendment under 37 C.F.R. § 1.116 of January 27, 1997, all amendments Appellants submitted before the final Office Action of April 14, 1998 (Paper No. 33) have been entered, resulting in claims 40-42 and 45-47. Appellants filed a Response After Final on July 14, 1998, and a Supplemental Amendment under 37 C.F.R. § 1.116 on August 5, 1998. The Examiner indicated in the Advisory Actions of June 24, 1998 (Paper No. 37) and August 31, 1998 (Paper No. 40), respectively, that these two responses after the final Office Action will be entered upon the filing of an Appeal Brief. Appendix I reflects these Amendments and contains the resulting pending claims on appeal.

V. Summary of Invention

Appellants will first summarize the claimed invention and will then explain the meaning of various claim terms. The claimed invention relates to Fab fragments that bind specifically to a venom of a snake of the Crotalus genus and that are essentially free from contaminating Fc as determined by immunoelectrophoresis using an anti-Fc antibody (claim 45). The claimed invention also relates to an antivenom composition comprising these Fab fragments (claim 40). The source of the Fab fragments can be Ig(G)T (claims 41 and 46), and the Ig(G)T can be polyvalent (claims 42 and 47).

An antivenom is a suspension of venom neutralizing antibodies that are prepared from the serum of animals (typically horses) that are hyperimmunized against a specific venom or venoms. (Specification at p. 4, lines 19-22). Typically, animals are

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repeatedly injected with increasing doses of venom, and the animals' sera are collected and used to obtain antibodies that can neutralize the venom. Antivenoms are typically used to treat human snake bite victims. (*See, Id.* at p. 23, lines 1-3).

An antibody molecule is commonly referred to as an immunoglobulin ("Ig") and is shaped like a "Y." (*Id.* at 2, lines 25-27). Exposing an antibody molecule to the enzyme pepsin results in the two upper arms of this "Y" splitting from the stem of the molecule but remaining attached to each other. This results in one $F(ab)_2$ fragment (the two upper arms attached to each other) and an Fc fragment (the stem). (*Id.* at lines 27-31.)

Exposing an antibody molecule to the enzyme papain results in the two upper arms of this "Y" splitting both from the stem of the molecule and from each other. (*Id.* at lines 41-43). This results in two separate Fab fragments (the two upper arms) and an Fc fragment (the stem). (*Id.* at lines 27-31).[1] The desired Fab fragments can then be purified by using an affinity column that separates the Fab fragments from the Fc fragments. (*Id.* at p. 7, lines 1-14; p. 8, line 37 through p. 9, line 4; Fig. 6; Fig. 8).

VI. Issues

Whether the Examiner properly made the following rejections:

A. rejection of claims 40-42 and 45-47 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification;

B. rejection of claims 40-42 and 45-47 under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al. as evidenced by Stedman's Medical Dictionary; and

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[1] "Fab" is sometimes written "F(ab)," and $F(ab)_2$ is sometimes written "$F(ab)_2$ or Fab'_2."

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C. rejection of claims 45-47 under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al.

The Examiner also rejected claims 40-42 in the final Office Action of April 14, 1998 under 35 U.S.C. § 112, first paragraph, because the specification allegedly did not provide an adequate written description for the recitation of "antivenom" (Paper No. 33 at p. 2). Appellants responded to this rejection on several grounds in the Response After Final of May 4, 1998. In the Advisory Action of June 24, 1998, the Examiner indicated that the Response would be entered upon filing an Appeal Brief and stated "the rejections as enunciated in the enclosed note remain for reasons of record." (Paper No. 37 at p. 1.) The "enclosed note," a complete Office Action, does not mention the previous rejection of claims 40-42 under 35 U.S.C. § 112, first paragraph, for an alleged lack of written description for the recitation of "antivenom." Since this rejection no longer remains, it is not an issue in this Appeal.

VII. Grouping of Claims

A. Claims 40-42 and 45-47 stand or fall together concerning the 35 U.S.C. § 112, first paragraph, written description rejection for purposes of this appeal only.

B. Claims 40-42 and 45-47 stand or fall together concerning the 35 U.S.C. § 103 rejection over Sullivan et al. in view of Coulter et al. and Smith et al. as evidenced by Stedman's Medical Dictionary for purposes of this appeal only.

C. Claims 45-47 stand or fall together concerning the rejection under 35 U.S.C. § 103 over Sullivan et al. in view of Coulter et al. for purposes of this appeal only.

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VIII. Argument

Appellants will address each of the three grounds of rejection in the order specified by 37 C.F.R. § 1.192(c)(8).

A. Rejection of Claims 40-42 and 45-47 under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 40-42 and 45-47 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification. Specifically, the Examiner contends that the specification does not support the recitation of "essentially free from contaminating Fc." The Examiner repeatedly states that the specification and original claims "do not recite that the claimed Fab are essentially free from contaminating Fc" because "[t]he specification discloses that the claimed F(ab) produced an electrophoresis wherein no precipitation band against anti-Fc antibodies is seen." (Paper No. 33 at p. 3, lines 3-6, 7-10; *see also* Paper No. 37 at p. 2, lines 7-10, 12-14.) Appellants respectfully request that the Board reverse this rejection because the specification does describe Fab fragments that are essentially free from contaminating Fc, and the Examiner has applied an impermissible literal support test for written description support.

1. The Specification Indicates the Claimed Invention Can Include Immaterial Amounts of Fc Fragments

The Examiner has observed correctly that the specification discloses Fab fragments that were free from contaminating Fc. (Paper No. 33 at p. 3, lines 7-10). More specifically, the embodiment reflected in Figure 2 shows that digesting an

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antibody molecule with papain for 48 hours results in Fab fragments that do not precipitate a band against anti-Fc antibodies. (Specification at sentence bridging pp. 16 and 17).

However, in another embodiment, the specification also states that when the papain is not allowed enough time to fully digest the antibody, a very small amount of Fc fragments may remain. More specifically, the specification states that digesting an antibody molecule with papain for only four hours results in fragments that produce, "a **slight hint** of a F(c) reaction." (*Id.* at 17, lines 27-28; emphasis added). This disclosure fully supports the recitation of "essentially free from contaminating Fc" in claims 40-42 and 45-47.

Since the written description requirement is directed to "a person skilled in art," 35 U.S.C. § 112, first paragraph, "the disclosure need only reasonably convey to persons skilled in the art that the inventor[s] had possession of the subject matter in question." *Fujikawa v. Wattanasin*, 39 U.S.P.Q.2d 1895, 1904 (Fed. Cir. 1996); *Ex parte Harvey*, 3 U.S.P.Q.2d 1626, 1628 (PTO Bd. Pat. App & Int'f. 1986). "How the specification accomplishes this is not material." *In re Alton*, 37 U.S.P.Q.2d 1578, 1581 (Fed. Cir. 1996) (quoting *In re Wertheim*, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976)). The specification would have conveyed to one skilled in the art that Appellants had possession of the claimed subject matter because the discussion of a "slight hint of a Fc reaction" on page 17 would have conveyed to one skilled in the art that Appellants had possession of Fab fragments "**essentially** free from contaminating Fc," as well as "free from contaminating Fc."

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That the specification does not devote more discussion to this aspect of the claimed invention in no way affects the adequacy of its written description. "Certainly no length requirement exists for a disclosure to adequately describe the invention." *In re Hayes Microcomputer Prods. Inc.*, 25 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1992). Rather, "the adequacy of the description of an invention depends on its content in relation to the particular invention, not its length." *Id.* As the specification describes, the claimed invention attempts to minimize the presence of Fc fragments, but the discussion of a "slight hint of a Fc reaction" indicates that it does not necessarily result in the total absence of Fc fragments.

The specification discusses two problems with previous antivenoms—an allergic reaction to extraneous horse proteins in the antivevom and an allergic reaction to the whole antibody. (*Id.* at p. 4, lines 35-40.) Dr. Findley E. Russell discussed this second problem (serum sickness) and its relationship to antibody fragments in his First Declaration. Soon after the development of the first antivenoms, doctors recognized that they could elicit serum sickness. (First Russell Decl. at ¶ 21.) Serum sickness occurs so often and is so dangerous that the leading commercial antivenom can only be obtained in a kit that also contains serum to test for serum sickness before administering the antivenom. (*Id.*)

In order to reduce serum sickness, Appellants produced an improved antivenom comprising Fab fragments by digesting immunoglobulins with papain and removing the Fc fragments, which are antigenic to humans. (Specification at p. 11, lines 21-26; p. 23, lines 17-21.) Specifically, Appellants took a known whole antivenom, purified its

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antibodies, and ran them over a column containing papain to digest the antibodies. (*Id.* at pp. 15-16.) Appellants then took the resulting solution of Fab and Fc fragments, ran the solution over an affinity column, and eluted off the resulting purified Fab fragments to separate the Fab fragments from the Fc fragments. (*Id.* at p. 16, lines 2-10).

Figure 2 shows the results of an immunoelectrophoresis used to detect contaminants in the resulting Fab solution obtained by digesting the known antivenom for 48 hours with papain. The immunoelectrophoresis shows no contaminating Fc fragments. (*Id.* at pp. 16-17; Fig. 2.)

Figure 4 shows the results of a second immunoelectrophoresis that differed from this first immunoelectrophoresis only in the amount of time the papain was allowed to digest the known antivenom. Unlike the 48-hour digest of Figure 2, Figure 4 involved a four-hour digest. (Specification at pp. 16-17; Fig. 4.) This four-hour papain digestion was weaker than the 48-hour digestion (specification at p. 17, line 5) in that the antibody molecules apparently were not 100% digested to Fab fragments. (*Id.* at line 28; Fig. 4.)

Given their goal of reducing serum sickness by removing Fc fragments from the Fab fragments, Appellants contemplated that papain digestions of longer than four hours might be preferred to remove all Fc fragments and obtain Fab fragments free from contaminating Fc fragments. (*Id.* at lines 34-35). However, Appellants also recognized that the slight hint of an Fc reaction seen with the four-hour digest was so small as to not be a major concern, so that their preferred digestion period included, as a lower limit, four hours. (*Id.*)

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Consideration of Appellants' description of their embodiment that permits the inclusion of some Fc fragments in relation to the claimed invention reveals that it would have conveyed that Appellants' invention attempts to reduce serum sickness by minimizing the presence of Fc fragments, but it does not necessarily result in the total absence of Fc fragments. In relation to Appellants' goal of reducing serum sickness by minimizing the contaminating Fc fragments, their indication that their preferred papain digestion period could result in "a slight hint of an Fc reaction," would have conveyed to one skilled in the art that Appellants invented Fab fragments essentially free from contaminating Fc as determined by electrophoresis using an anti-Fc antibody and that they had invented an antivenom comprising such Fab fragments.

2. The Specification Did Not Need to Use The Claim Term "Essentially"

The Federal Circuit, the Court of Customs and Patent Appeals, the Board, and the Patent and Trademark Office, have all repeatedly rejected any requirement that the specification use the same words that the claims use. *See, e.g.*, *Alton*, 37 U.S.P.Q.2d at 158, 159 (rejecting *ipsis verbis* and explicit description requirements); *In re Herschler*, 20 U.S.P.Q. 711, 717 (C.C.P.A. 1979)(rejecting *haec verba* requirement); *Ex parte Yamaguchi*, 16 U.S.P.Q.2d 1805, 1807 (PTO Bd. Pat. App. & Int. 1988)(rejecting *ipsis verbis* requirement); M.P.E.P. § 2163.02, p. 2100-141 (7th Ed. 1998)(rejecting *haec verba* requirement). Despite the clear rejection of a literal support requirement for an adequate written description, an examination of the Examiner's language in the final

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Office Action shows that the Examiner rejected claims 40-42 and 45-47 on this very basis. For example, the Examiner stated:

> The specification and original claims 27 and 29 **do not recite** that the claimed F(ab) are essentially free from contaminating F(c). They **recite** that the claimed F(ab) produce an electrophoresis wherein no precipitation band against anti-Fc antibodies is seen.

(Paper No. 33 at 3, lines 2-5; emphasis added). The Examiner makes the same point in the very next paragraph:

> [t]here is **no disclosure** in the specification as originally filed that the claimed F(ab) are essentially free from contaminating Fc. The specification **discloses** that the claimed F(ab) produce an electrophoresis wherein no precipitation band against anti-Fc antibodies is seen.

(Paper No. 33 at 3, lines 6-9; emphasis added).

In the Advisory Action of June 24, 1988, the Examiner again relied upon these same reasons for maintaining the rejection

> The specification and original claims 27 and 29 **do not recite** that the claimed F(ab) are essentially free from contaminating F(c). They **recite** that the claimed F(ab) produce an electrophoresis wherein no precipitation band against anti-Fc antibodies is seen.

(Paper No. 37 at 2, lines 7-10; emphasis added). Once again, the Examiner made the same point in the very next paragraph:

> [t]here is **no disclosure** in the specification as originally filed that the claimed F(ab) are essentially free from contaminating Fc. The specification **discloses** that the claimed F(ab) produce an electrophoresis wherein no precipitation band against anti-Fc antibodies is seen.

(Paper No. 37 at 2, lines 11-14; emphasis added).

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By repeatedly emphasizing that the specification does not contain the specific phrase "essentially free from," the Examiner appears to have applied an improper literal support requirement. Since a literal support requirement for an adequate written description has been uniformly rejected, Appellants respectfully request that the Board reverse this rejection.

Although the specification does not expressly use it, the adverb "essentially" has long been recognized in patent law as including elements that "do not **materially** affect the **basic** and **novel** characteristic" of the claimed invention when nonrecited elements are otherwise excluded from a claim by a closed transitional phrase. (*See* M.P.E.P. § 2111.03 (citing *In re Hoechst*, 190 U.S.P.Q. 461, 463 (C.C.P.A. 1976); emphasis added). Thus, "essentially free from" opens claims to elements that do not materially affect the basic and novel characteristics of the claimed invention. In this case, the presence of minor amounts of contaminating Fc that do not materially affect the basic and novel characteristics of the claimed invention, such as the slight trace of the 4 hour digest, are encompassed by the claims. In other words, Fc may be present in detectable levels, but it may not be present in levels that result in serum sickness. (*See, e.g.*, specification at 11, lines 11-29).

Appellants have shown that the specification would have conveyed to one skilled in the art that they invented Fab fragments that had immaterial amounts of contaminating Fc fragments and that they invented an antivenom containing such Fab fragments. Appellants have also shown that the specification's conveyance to one skilled in the art that Appellant had invented such Fab fragments and such an

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antivenom support the recitation of "essentially free from" contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies. Accordingly, Appellants respectfully request reversal of the rejection of claims 40-42 and 45-47 under 35 U.S.C. § 112, first paragraph.

B. Rejection of Claims 40-42 and 45-47 under 35 U.S.C. § 103

The Examiner rejected claims 40-42 (the antivenom claims) and 45-47 (the Fab fragment claims) under 35 U.S.C. § 103 as allegedly being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al., as evidenced by Stedman's Medical Dictionary. Specifically, the Examiner asserted that it would have been obvious to one of ordinary skill in the art to use Sullivan et al's purified antivenom against venom of the Crotalus genus to produce antivenom compositions comprising Fab fragments using Coulter et al's method for producing Fab fragments free of Fc fragments based upon Smith et al.'s success with Fab fragments to digoxin. (Paper No. 21 at pp. 3-4.)[2] The Examiner relies upon Stedman's Medical Dictionary for the definition of "antivenom."

Sullivan *et al.* used affinity chromatography to isolate and purify whole antibody molecules from antivenom preparations. Coulter *et al.* digested whole antibody to the toxin textilotoxin with papain to form Fab fragments and found that their Fab fragments and the whole antibody molecules "were equivalent" in their ability to neutralize textilotoxin in rabbits. (Coulter *et al.* at p. 202.) Smith *et al.* digested whole antibody to

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[2] The Examiner has relied upon this reasoning in all subsequent Office Actions, including the final Office Action of April 14, 1998. (*See, e.g.,* Paper No. 33 at pp. 3-4.)

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the toxin digoxin to form Fab fragments and found that their Fab fragments were distributed and excreted more rapidly than whole antibody molecules in rabbits. (Smith *et al.* at 384.)

According to the Examiner, one of ordinary skill in the art would have been motivated to combine the Sullivan et al., Coulter et al., and Smith et al. references because Smith et al. teaches the advantages of Fab fragments over whole antibodies for the neutralization and clearance of toxic substances. (*Id.*) Appellants respectfully request that the Board reverse this rejection because the Examiner relied upon his hindsight belief that the claimed invention is obvious when the evidence shows the absence of a reasonable expectation of success at the time of Appellants' invention.

1. One Skilled in The Art Would Not Have Predicted That Results With a Single Venom Toxin (such as Coulter et al.'s) Could Be Extrapolated to Whole Venoms

Appellants will first address the Coulter *et al.* reference because the Examiner appears to have consistently misunderstood both its teachings and Appellants' evidence of the lack of an expectation of success based upon the Coulter *et al.* reference.

Coulter *et al.* used textilotoxin, the primary toxin in the venom of the Australian brown snake (*Pseudonaja textilis*). (Coulter *et al.* at p. 199, last sentence; First Russell Decl. at ¶ 46.) The pending claims recite a snake of the genus Crotalus, a genus of the family Crotalidae. As can be seen from its name, the snake Coulter *et al.* used is not a member of the genus Crotalus, nor is it even of the same family as the Crotalus genus. Rather, it is a member of the genus *Pseudonaja*. (Coulter *et al.* at 199.) Indeed,

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Coulter *et al.'s* snake is an elapid (Russell (1996) Toxic Effects of Animal Toxins. In *Casarett and Doull's Toxicology*: *The Basic Science of Poisons*, (5th Ed.) at p. 802 (attached as Exhibit 10 to the First Russell Declaration)), and the elapids are of the family Elapidae, not Crotalidae. (*Snake Venom Poisoning* at p. 5.)

Furthermore, while it might now appear to the Examiner, after having read Appellants' disclosure, to be obvious to combine Coulter *et al.'s* teaching concerning Fab fragments with Sullivan *et al.'s* antivenom, "hindsight is not a justifiable basis on which to find" that an invention was obvious. *Amgen v. Chugai Pharm. Co. Ltd.*, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Rather, the prior art, not Appellants' disclosure, must have provided a reasonable expectation of success. *Id.* at 1022; *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). This rejection, however, depends upon a hindsight-aided application of the teachings from Appellants' disclosure, not the prior art. The evidence Appellants have submitted shows that this rejection fails for a lack of the required expectation of success.

Textilotoxin is simply **a single toxin** from Australian brown snake venom. Although venoms can be simple substances, as in some marine animals, in snakes they are often very complicated mixtures of many individual toxins. (First Russell Decl. at. ¶ 15, ¶ 47; Smith Decl. at ¶ 6.) In some venoms of Crotalus snakes, there may be 100 different protein fractions. (First Russell Decl. at ¶ 15.) Due to their complexity, the full composition of snake venoms is unknown. (*Id.*) Not only is the composition of snake venoms complicated and their exact composition unknown, but the pharmacological effects of some constituent toxins are unknown. (*Id.* at ¶ 16.)

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Due to the unknown composition of snake venoms and the unknown effect of even the identified toxins in snake venoms, basic toxicology texts caution against extrapolating results from individual venom toxins (like Coulter *et al.'s*) to whole venoms (like the claims recite). (*Toxic Effects of Animal Toxins* at p. 802; *Snake Venom Poisoning* at p. 168.) Accordingly, the Examiner is incorrect in attempting to extrapolate Coulter *et al.'s* results with Fab fragments to a single snake venom toxin to the results that would have been expected with Fab fragments to an entire snake venom comprising many unknown toxins of unknown effect. As Dr. Russell stated, "one would not have expected Coulter *et al.'s* results with Fab to a single **toxin** to predict similar results with Fab to a Crotalidae snake **venom**, including a Crotalus snake **venom**." (First Russell Decl. at ¶ 47; emphasis in original.)

Since Coulter *et al.* used Fab fragments to a toxin from the venom of a snake of a different genus than the claims recite, and since one of ordinary skill in the art would not have expected results with Fab fragments to a single venom toxin to predict what would occur with Fab fragments to an entire Crotalus venom, any rejection relying upon the Coulter *et al.* reference must fail. Not only was there no reasonable expectation of success based upon the Coulter et al. reference before Appellants' invention, there was no reasonable expectation of success in using Fab antivenom fragments based upon <u>any</u> references, including Sullivan et al., Coulter et al., and Smith et al.

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2. Befor Appellants' Invention, Fab Fragments Were Expected to Be Ineff ctive

Appellants submitted numerous references and the Declarations of Dr. Damon Smith, Dr. John B. Sullivan, and Findley E. Russell, M.D., Ph.D., which prove that, while the claimed invention might now appear to the Examiner, in hindsight, to be obvious, at the time of Appellants' invention, the claimed invention would not have been obvious because one of ordinary skill in the art would not have had a reasonable expectation of success. Indeed, Dr. Sullivan "and others questioned whether anti-venom F(ab)'s would be effective [antivenoms]" (Sullivan Decl. at ¶ 9), and Dr. Sullivan and others actually believed that Fab fragments would "fail or **increase** toxicity of the venom." (Sullivan Decl. at ¶ 13; emphasis in original.)

The only commercially available antivenom at the time of Appellants' invention for North American snakes of the Crotalus genus was Antivenin [Crotalidae] Polyvalent (equine origin) ("ACP"), which first became available in 1947. (First Russell Decl. at ¶ 20; Smith Decl. at ¶ 7.) This antivenom suffers the serious problem suffered by other antivenoms of often causing serum sickness, an allergic reaction to the antivenom that is sometimes as deleterious as the venom. (First Russell Decl. at ¶ 20; specification at p. 4, lines 35-40.) Over 75% of envenomation patients who receive ACP suffer from serum sickness. (First Russell Decl. at ¶ 20.) This danger can be so great that physicians may not administer this antivenom for some cases of envenomation, and ACP can only be obtained in a kit that also contains test serum for possibly detecting serum sickness. (*Id.*)

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Because of the serious problem of serum sickness, extensive research had been performed on developing better antivenoms. (First Russell Decl. at ¶ 24.) As Appellants discussed above, it was generally believed that "given possession of the antibody active site, the smaller the antibody molecule, the better. (Specification at p. 3, lines 1-2.) Thus, much of this research focused on immunoglobulin fragments, which may not provoke an immune reaction. (First Russell Decl. at ¶ 24.) In the late 1960's, researchers began experimenting with antivenoms comprising $F(ab)_2$ fragments, and such antivenoms first became commercially available in 1969. (*Id.*; Smith Decl. at ¶ 7.) Although the smaller size of the $F(ab)_2$ fragments results in less serum sickness, such antivenoms appear less effective than antivenoms comprising whole immunoglobulin. (First Russell Decl. at ¶ 25.) Consequently, Crotalidae antivenoms comprising $F(ab)_2$ fragments were not produced in the United States. (First Russell Decl. at ¶ 24).

Although serum sickness had long been recognized as a major problem with antivenoms, and although smaller antibody fragments had long been known to be less immunogenic, no researcher developed antivenoms comprising the smaller Fab fragments prior to Appellants' invention. (*Id.* at ¶ 25; Sullivan Decl. at ¶ 5.) Indeed, there had been no significant improvements in commercial antivenoms since 1969, when an $F(ab)_2$ antivenom was commercially sold. (Smith Decl. at ¶ 7.) Development of antivenoms comprising antibody fragments halted at the larger $F(ab)_2$ fragments because the larger $F(ab)_2$ fragments appeared to some of ordinary skill in the art to be less effective than whole antibody. (First Russell Decl. at ¶ 25.)

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Not only did the $F(ab)_2$ fragments, which are larger than Fab fragments, appear to be less effective than whole antibody molecules, but those of ordinary skill in the art expected Fab fragments to be even less effective than the disappointing $F(ab)_2$ fragments for several reasons. (First Russell Decl. at ¶ 26; Sullivan Decl. at ¶ 5; Smith Decl. at ¶ 9.) First, Fab fragments cannot stearically hinder the binding of a venom protein to its tissue target as well as $F(ab)_2$ fragments because Fab fragments have only one active site. (First Russell Decl. at ¶ 29; Sullivan Decl. at ¶ 8.) The two binding sites on $F(ab)_2$ fragments allow them to bind to repeating antigenic determinants on a venom antigen, and this repetitive determinant binding stearically hinders the venom antigen from binding to its active site.

Second, since $F(ab)_2$ fragments contain two antigen binding sites, each individual $F(ab)_2$ fragment can bind two antigens. (Steward Sell, *Basic Immunology: Immune Mechanisms in Health and Disease*, at p. 89, Fig. 6-3 (1987).) As more $F(ab)_2$ fragments cross-link more antigens, they form larger complexes which, eventually, become large enough that they precipitate from solution. *Id.* In contrast, since Fab fragments have only one antigen binding site, they cannot form cross-linked complexes and precipitate the antigens. (Smith Decl. at ¶ 9.)

Third, those of ordinary skill in the art expected that Fab fragments would not be effective because they would be cleared before the venom. Many venom toxins are large, hydrophobic molecules, and they are usually injected deep into subcutaneous tissues. (First Russell Decl. at ¶ 30; Smith Decl. at ¶ 8.) These individual toxins are released slowly from the injection site, resulting in the "venom depot effect" whereby the venom toxins continue to be released into the circulatory system long after the initial

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bite. (First Russell Decl. at ¶ 30; Smith Decl. at ¶ 8.) Venom protein continues to be released from the injection site for weeks (Sullivan Decl. at ¶ 5(a)), and has been detected in a patient 46 days after envenomation. (Owenby et al., *Southern Medical Journal* (1990).)

Fab fragments have a molecular weight of around 45-55 Kd. (First Russell Decl. at ¶ 31.) This relatively small size allows the renal system to remove Fab fragments, resulting in a half-life of about 17 hours. (*Id.*) Indeed, the renal system completely eliminates Fab fragments in only 24-26 hours. (*Id.*)

$F(ab)_2$ fragments, in contrast, are about twice as large as Fab fragments–too large for the renal system to remove them. (*Id.* at ¶ 32.) Thus, they have a much longer half-life than Fab fragments, approximately 50 hours versus approximately 17 hours. (*Id.*) Given the renal system's rapid removal of Fab fragments, especially compared to $F(ab)_2$ fragments, and the venom depot effect, those of ordinary skill in the art expected that there would be no remaining Fab fragments to neutralize later-released venom toxins. (*Id.* at ¶ 32; Smith Decl. at ¶ 8.)

3. Before Appellants' Invention, Fab Fragments Were Actually Expected to Be Harmful

Not only did those of ordinary in the skill in the art believe that Fab fragments would be ineffective before Appellants' invention, they actually expected that such an antivenom could increase the lethality of the snake venom by redistributing and concentrating its toxins. (Russell Decl. at ¶ 33; Sullivan Decl. at ¶ 13.) The binding of

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Fab fragments and venom toxins is a dynamic process, having an equilibrium where individual venom toxins are constantly bound and released. (First Russell Decl. at ¶ 34.) The renal system's rapid removal of Fab fragments, however, continually decreases the number of Fab fragments remaining to bind the venom toxins. (Smith Decl. at ¶ 8.) Those of ordinary skill in the art were concerned that Fab fragments would bind venom toxins that were released into the circulatory system and then release the venom toxins at another site, perhaps concentrating the venom toxins in areas of high blood flow like the kidneys, heart, nervous system, and lungs. (First Russell Decl. at ¶ 36; Sullivan Decl. at ¶ 5(b).) As Dr. Sullivan stated,

> I and others maintained and discussed our concerns that F(ab) [fragments] would redistribute toxic venom proteins throughout the body, thus producing venom pathology at tissue sites and organ systems not typically seen in patients treated with [whole antibodies] or $F(ab)_2$.

(Sullivan Decl. at ¶ 7.) While the toxins might have caused swelling and local necrosis at the site of envenomation, the predicted redistribution and concentration of venom toxins might result in "coagulopathy, direct cardiotoxicity, liver and kidney damage, potential central nervous system, and peripheral nervous system damage." (*Id.*) Thus, what had been a systemic toxicity with venom toxins being released slowly into the circulation could become a localized toxicity with venom toxins being concentrated in the kidneys, heart, nervous system, and lungs by this "taxi" effect. (First Russell Decl. at ¶ 36; Sullivan Decl. at ¶ 5(a).)

This taxi effect was predicted, and it was a reason why those of ordinary skill in the art did not progress beyond the known $F(ab)_2$ fragments to the smaller Fab fragments. (Sullivan Decl. at ¶ 7.) According to Dr. Sullivan, the use of Fab fragments

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to treat envenomation would have been "medically unsound and contraindicated." (*Id.* at ¶ 13.) The belief of those of ordinary skill in the art that Fab fragments would actually increase the lethality of snake venom by concentrating high molecular weight snake toxins in areas of high blood flow was not a merely theoretical concern, as Faulstich *et al.* later demonstrated.

Faulstich *et al.* (Strongly Enhanced Toxicity of the Mushroom Toxin α-Amanitin by an Amatoxin-Specific Fab or Monoclonal Antibody. 26 *Toxicon* 491 (1988) (copy attached as Exhibit 7 to first Russell Declaration)) conducted a series of studies attempting to treat α-amatoxin poisoning with Fab fragments. Alpha-amatoxin is a high molecular weight toxin that is similar to some snake venom toxins. (First Russell Decl. at ¶ 37.) As a high molecular weight toxin, α-amatoxin cannot be cleared by the renal system. (*Id.*) Rather, like many snake toxins, it is cleared by the liver. (*Id.*) Since α-amatoxin is concentrated in the liver after oral ingestion, it is primarily toxic to liver cells. (*Id.*)

Faulstich *et al.* discovered that the Fab fragments did not decrease the toxicity of α-amatoxin in mice, but rather increased the toxicity of α-amatoxin by a factor of 50. (*Faulstich et al.* at p. 497.) Furthermore, the Fab fragments resulted in α-amatoxin being specifically toxic to kidney cells rather than liver cells. (*Id.*) This is exactly what one of ordinary skill in the art would have predicted. (First Russell Decl. at ¶ 38.) The Fab fragments bound the high molecular weight α-amatoxin, and then unbound it in their state of equilibrium at sites of high blood flow. (*Id.*) This unbinding at sites of high blood flow, especially the kidneys, resulted in the α-amatoxin being concentrated in

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these tissues and killing them. (*Id.*) Thus, Fab fragments greatly increased the toxicity of this high molecular weight toxin by concentrating it in areas of high blood flow.

Faulstich *et al's* results with Fab fragment directed to a high molecular weight toxin stood in contrast to Balthazar *et al.'s* results with Fab fragments to the low molecular weight toxin digoxin. (Balthazar *et al.* (1994) Utilization of Antidrug Antibody Fragments for the Optimization of Intraperitoneal Drug Therapy: Studies Using Digoxin as a Model Drug. *J. Pharm. Exp. Ther.* 268, 734 (attached at Exhibit 8 to the First Russell Declaration).) Digoxin is unlike most Crotalidae venom toxins; it is a very small molecule; small enough that the renal system can clear the Fab-digoxin complex. (First Russell Decl. at ¶ 39; Smith Decl. at ¶¶ 8, 10.) Since the renal system can filter the Fab-digoxin complex, the Fab fragments did not redistribute and concentrate digoxin, as one of ordinary skill in the art would have predicted. (First Russell Decl. at ¶ 39.) Accordingly, Balthazar *et al.* found that F(ab) fragments effectively treated digoxin toxicity, just as Smith *et al.*, upon which the Examiner relies, found.

However, Balthazar *et al.* recognized the potential problems of Fab therapy for large toxins, like α-amatoxin and some Crotalidae venom toxins:

> First, the alteration of drug distribution which accompanies antibody drug complexation may result in a **potentiation of drug toxicities** or the development of **new drug toxicities in certain cases** . . . . The risk of **redistributing systemic toxicity**, rather than minimizing systemic toxicity, should be appreciated as a potential outcome of the proposed approach.

(Balthazar *et al.* at p. 738, cols. 1-2; emphasis added.)

Accordingly, those of ordinary skill in the art were concerned that treatment with an antivenom comprising Fab fragments would actually be harmful for the treatment of

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high molecular weight venom toxins because the Fab fragments would redistribute high molecular weight toxins to areas of high blood flow, creating new toxicities. Faulstich *et al.* confirmed this concern with a toxin that is of a similar molecular weight as many snake venom toxins. (First Russell Decl. at ¶ 41.) Balthazar *et al.* reinforced this concern by showing that this effect did not occur with a low molecular weight toxin that the renal system could clear as part of an Fab-toxin complex. (First Russell Decl. at ¶ 42.) Indeed, despite the effectiveness of their treatment, Balthazar *et al.* specifically discussed their concern that Fab fragments might alter drug toxicities or redistribute systemic toxicities.

These *in vivo* mechanisms that led those of ordinary skill in the art to expect that the claimed invention would not be effective show that the Examiner's reliance upon the Coulter *et al.* reference for teaching that Fab fragments have a higher sensitivity than whole antibody in *in vitro* tests is misplaced. Coulter *et al.* did not treat envenomation with their Fab fragments. Rather, Coulter *et al.* first mixed textilotoxin with their Fab fragments *in vitro*. (Coulter *et al.* at p. 201, 3rd full paragraph.) Coulter *et al.* then injected the already bound Fab-textilotoxin complex intravenously. This treatment with Fab fragments resulted in neutralization that was essentially equivalent to the treatment with the IgG fragments, just as one of ordinary skill in the art would have expected. (First Russell Decl. at ¶ 48.) Since the Fab-textilotoxin mixture was first mixed *in vitro* and then injected intravenously, the Fab did not have the opportunity to redistribute and concentrate the textilotoxin in high blood flow parts. (*Id.*) Accordingly, the Coulter *et al.* reference would not have provided a reasonable expectation of success for an

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antivenom comprising Fab fragments to any venom toxins, despite the Examiner's assertion to the contrary. (*Id.*)

Once again, this was not a merely theoretical concern, as Sorkine *et al.* later demonstrated. Sorkine *et al.* conducted a similar experiment in 1983 by mixing Fab fragments with a snake venom before injecting the mixture into a mouse, and they obtained similar results. (Sorkine *et al.* (1995) Comparison of $F(ab')_2$ and Fab Efficiency on Plasma Extravasation Induced *Viper aspis* Venom. *Toxicon* 33, 257 (attached as Exhibit 11 to the First Russell Declaration).) This treatment resulted in a considerable reduction in capillary permeability. However, the Fab fragments were much less effective when they were administered *in vivo* separately from the venom. As Sorkine *et al.* state "these data showed firstly that the *in vitro* neutralization of the venom by immunoglobulin fragments does not reflect their *in vivo* efficiency." (Sorkine *et al.* at 257.) Thus, the Sorkine *et al.* reference shows that one would not have expected Coulter *et al.*'s *in vitro* neutralization results to predict the effectiveness of antivenoms comprising Fab fragments *in vivo*. (First Russell Decl. at ¶ 50.)

In sum, prior to Appellants' invention, those of ordinary skill in the art did not have a reasonable expectation of success that an antivenom comprising Fab fragments to Crotalidae venom would be effective. Obviousness requires that "[b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not [Appellants'] disclosure," *Vaeck*, 20 U.S.P.Q.2d at 1442, and Appellants have shown that that is not the case here. Despite the known problems with the commercially available venom for Crotalidae envenomation since 1947, and the well-

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known fact that smaller immunoglobulin fragments are less immunogenic, those of ordinary skill in the art had not progressed beyond antivenoms comprising the disappointing $F(ab)_2$ fragments to the smaller Fab fragments because they expected Fab fragments to be not just ineffective, but actually more harmful to the patient that no treatment at all. For these reasons, Appellants respectfully request that the Board reverse the rejections of claims 40-42 and 45-47 under 35 U.S.C. § 103.

C. Rejection of Claims 45-47 Under 35 U.S.C. § 103

The Examiner rejected claims 45-47 (the Fab fragment claims) under 35 U.S.C. § 103 as allegedly being unpatentable over Sullivan *et al.* in view of Coulter *et al.* Specifically, the Examiner asserted that Sullivan *et al.* teach an antivenom comprising whole antibody against venom of a snake of the Crotalus genus and that Coulter *et al.* teach that Fab fragments that are free from contaminating Fc fragments are more sensitive than whole antibody when used in an *in vitro* assay. (Paper No. 31 at pp. 8-9.) Appellants respectfully request that the Board reverse this rejection because the Examiner again improperly relied upon his hindsight belief that the claimed invention is obvious, when the evidence shows the absence of a reasonable expectation of success at the time of Appellants' invention.

Again, "hindsight is not a justifiable basis on which to find" that an invention was obvious. *Amgen,* 18 U.S.P.Q.2d at 1023. Rather, at the time of the invention, there must have been a reasonable expectation of success, and that expectation must come from the prior art, not Appellants' disclosure. *Id.* at 1022.

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Appellants showed above that the combination of Sullivan et al., Coulter et al., and Smith et al. does not render claims 45-47 (the Fab fragment claims), as well as claims 40-42 (the antivenom claims), obvious because there would not have been a reasonable expectation of success. Since the combination of these three references does not render claims 45-47 obvious, the combination of only Sullivan et al. and Coulter et al. cannot render claims 45-47 obvious.

While it might now appear to be obvious to combine Coulter *et al.'s* teaching concerning Fab fragments with Sullivan *et al.'s* antivenom, "hindsight is not a justifiable basis on which to find" that an invention was obvious. *Amgen,* 18 U.S.P.Q.2d at 1023. Rather, the prior art, not Appellants' disclosure, must have provided a reasonable expectation of success. *Id.* at 1022; *Vaeck*, 20 U.S.P.Q.2d at 1442. This rejection, however, also depends upon a hindsight-aided application of the teachings from Appellants' disclosure, not the prior art. The evidence Appellants have submitted shows that this rejection lacks the required expectation of success.

As Appellants showed above, Coulter et al. used a venom toxin from a snake of a genus *(Pseudonaja)* different from the genus the pending claims recite (*Crotalus*). More importantly, Coulter *et al.* used a single venom toxin, not an entire venom, and basic toxicology texts caution against extrapolating from results with single venom toxins (like Coulter et al's) to whole venoms (like the claims recite). (*Toxic Effects of Animal Toxins* at p. 802; *Snake Venom Poisoning* at p. 168.) Thus, one of ordinary skill in the art "would not have expected Coulter *et al's* results with Fab to a single **toxin** to predict similar results with Fab to a Crotalidae snake **venom**; including a Crotalus

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snake **v nom** (First Russell Decl. at ¶ 47; emphasis in original), as the Examiner has alleged.

Sullivan cannot remedy the deficiencies of Coulter et al. Even the Examiner has not suggested that Sullivan et al. contains any teaching or suggestion concerning Fab fragments. Since the evidence shows that, before Appellants' invention, there would not have been a reasonable expectation of success, Appellants respectfully request that the Board also reverse the rejection of claims 45-47 under 35 U.S.C. § 103.

IX. CONCLUSION

In view of the forgoing reasons, Appellants respectfully request that the rejection of the pending claims under 35 U.S.C. § 112, first paragraph, and the two rejections of the pending claims under 35 U.S.C. § 103 be reversed.

If further extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such an extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 that are not enclosed herewith, including any

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fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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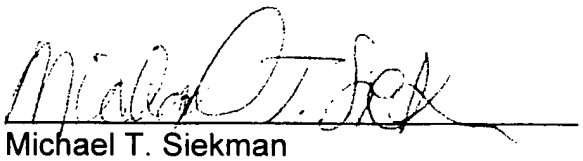
By: 

Michael T. Siekman
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Dated: February 12, 1999

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APPENDIX I

40. An antivenom composition comprising Fab fragments which bind specifically to a venom of a snake of the Crotalus genus and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically acceptable carrier.

41. The antivenom composition of claim 40, wherein an antibody source for said Fab fragments is IgG(T).

42. The antivenom composition of claim 40, wherein an antibody source for said Fab fragments is polyvalent IgG(T).

45. Fab fragments which bind specifically to a venom of a snake of the Crotalus genus, and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using an anti-Fc antibody.

46. The Fab fragments of claim 45, wherein an antibody source for said Fab fragments is IgG(T).

47. The Fab fragments of claim 45, wherein an antibody source for said Fab fragments is polyvalent IgG(T).

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Filed 5/6/99

PATENT
Attorney Docket No. 4249.0002-05

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	)	
	)	
John B. SULLIVAN et al.	)	
	)	
Serial No. 08/405,454	)	Group Art Unit: 1644
	)	
Filed: March 15, 1995	)	Examiner: Ron Schwadron, Ph.D.
	)	
For: ANTIVENOM COMPOSITION CONTAINING FAB FRAGMENTS (As Amended)	)	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

APPELLANTS' AMENDED BRIEF
IN SUPPORT OF APPEAL UNDER 37 C.F.R. § 1.192

In response to the Notification of Non-Compliance of April 21, 1999 (Paper No. 43), and pursuant to 37 C.F.R. § 1.192, Appellants submit this Amended Appeal Brief in triplicate to the Board of Patent Appeals and Interferences in support of their Appeal from the Final Office Action dated April 14, 1998 (Paper No. 33). Appellants initiated this Appeal from the final rejection of claims 40-42 and 45-47 by filing a Notice of Appeal on July 14, 1998, along with the fee required by 37 C.F.R. § 1.17(b). As an Appeal Brief, thus, became due on September 14, 1998, Appellants filed a Petition for a Five-Month Extension of Time and an Appeal Brief (in triplicate) on February 12, 1999.

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Notification of Non-Complianc

The Patent and Trademark Office mailed a Notification of Non-Compliance under 37 C.F.R. § 1.192(c) on April 21, 1999. In the Notification, the Examiner asserted that: (1) the Appeal Brief does not contain the items required under 37 C.F.R. § 1.192(c) or the items are not under the proper heading or not in the proper order (item 1); (2) the Appeal Brief improperly addresses the "Amendment After Final filed 5/4/98" (item 2); and (3) a single ground of rejection has been applied to two or more claims and the brief includes the statement required by 37 C.F.R. § 1.192(c)(7) that one or more claims do not stand or fall together but does not present arguments in support thereof (item 3).

Appellant respectfully disagrees with each of these assertions. First, the Appeal Brief does contain all the items required by 37 C.F.R. § 1.192(c); they are under the proper headings; and they are in the appropriate order.

Second, the Appeal Brief did not address the "Amendment After Final filed 5/4/98" because it was a "Response," not an "Amendment." As a response, it did not attempt to amend any claims. The rule expressly refers to "Amendments," and the purpose of the rule is "to avoid confusion as to which claims are on appeal, and the precise wording of those claims, particularly where the appellant has sought to amend claims after final rejection." M.P.E.P. § 1206, page 1200-8, 2d col. Accordingly, Appellants correctly did not address the status of the Response After Final in Appeal Brief.

Third, the Appeal Brief does not contain arguments supporting any statement under 37 C.F.R. § 1.192(c)(7) that one or more claims facing the same appealed

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rejection stand or fall together, because the Appeal Brief does not contain any such statement. As the Appeal Brief indicates, Appellants are appealing three rejections. For each of these three rejections, Appellants not only did not state that the claims did not stand or fall together, Appellants affirmatively stated that the claims did stand or fall together.

The undersigned discussed the Notification of Non-Compliance with Examiner Ronald B. Schwadron, Ph.D. by telephone on May 5, 1999. Examiner Schwadron indicated that item 1 on the Notification of Non-Compliance was checked because items 3 and 6 were checked. The undersigned made the above arguments regarding items 3 and 6. Examiner Schwadron indicated that he would have to examine M.P.E.P. § 1206 regarding item 3 and agreed with the undersigned's arguments regarding item 6. To expedite consideration of the Appeal Brief, however, it was agreed that Appellant would submit an Amended Appeal Brief setting forth these arguments for the record and addressing the status of the Response After Final.

This application is a continuation of application Serial No. 08/277,288, filed July 22, 1994, which is a continuation of application Serial No. 07/124,438, filed September 22, 1993, which is a continuation of application Serial No. 07/593,271, filed October 1, 1990, which is a division of application Serial No. 07/378,925, filed July 12, 1989, which is a division of application Serial No. 06/659,629, filed October 9, 1984, now U.S. Patent No. 4,849,352, issued July 18, 1989.

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I. Real Party in Interest

The real party in interest in the pending appeal is the Assignee, Therapeutic Antibodies, Inc. of Nashville, Tennessee, by virtue of an assignment from Appellants, duly recorded.

II. Related Appeals and Interferences

Appellants, the undersigned, and the assignee know of no other appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in this Appeal.

III. Status of Claims

Appendix I contains the pending claims on appeal (40-42 and 45-47).

Applicants filed parent application Serial No. 07/124,438 with claims 1-30 and canceled claims 1-16 in the papers filing divisional application Serial No. 07/378,925. Appellants then filed the Preliminary Amendment of October 1, 1990, in divisional application Serial No. 07/593,271, canceling claims 17-19 and amending claims 20-26. Appellants then filed a Preliminary Amendment in application Serial No. 08/124,438 on December 16, 1993; amending claims 27, 29, and 30; canceling claims 20-26 and 28, and adding claims 31-39, resulting in claims 27 and 29-39 being pending.

Appellants amended claims 27 and 29 and canceled claims 30-36 in the Amendment of January 17, 1995, in application Serial No. 08/277,288 resulting in claims 27, 29, and 37-39 being pending. Appellants amended claims 27 and 29 in the

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Preliminary Amendment of October 5, 1995. Appellants then canceled claims 27, 29, and 37-39 and added new claims 40-49 in the Amendment of April 30, 1996, resulting in claims 40-49 being pending.

Appellants proposed amending claims 40-49 in the Amendment under 37 C.F.R. § 1.116 of January 27, 1997, but the Examiner did not enter the Amendment in the Advisory Action of February 12, 1997. Appellants amended claims 40-49 in the Amendment under 37 C.F.R. § 1.129(a) of April 15 1997.

Appellants canceled claims 43-44 and 48-49 and amended claims 40-45 in the Amendment of December 19, 1997, resulting in claims 40-42 and 45-47. Finally, Appellants proposed amending claims 41-42 in the Supplemental Amendment under 37 C.F.R. § 1.116 of August 5, 1997. The Examiner indicated that this Amendment would be entered upon the filing of an Appeal Brief in the Advisory Action of August 31, 1998 (Paper No. 40). Accordingly, claims 40-42 and 45-47 as Appellants reproduce in Appendix I, are pending in this application.

IV. Status of Amendments

Other than the amendments Appellants proposed in the Amendment under 37 C.F.R. § 1.116 of January 27, 1997, all amendments Appellants submitted before the final Office Action of April 14, 1998 (Paper No. 33) have been entered, resulting in claims 40-42 and 45-47. Appellants filed a Response After Final on May 4, 1998, and a Supplemental Amendment under 37 C.F.R. § 1.116 on August 5, 1998. The Examiner indicated in the Advisory Actions of June 24, 1998 (Paper No. 37) and August 31, 1998

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(Paper No. 40), respectively, that response and the amendment after the final Office Action will be entered upon the filing of an Appeal Brief. Appendix I reflects these Amendments and contains the resulting pending claims on appeal.

V. Summary of Invention

Appellants will first summarize the claimed invention and will then explain the meaning of various claim terms. The claimed invention relates to Fab fragments that bind specifically to a venom of a snake of the Crotalus genus and that are essentially free from contaminating Fc as determined by immunoelectrophoresis using an anti-Fc antibody (claim 45). The claimed invention also relates to an antivenom composition comprising these Fab fragments (claim 40). The source of the Fab fragments can be Ig(G)T (claims 41 and 46), and the Ig(G)T can be polyvalent (claims 42 and 47).

An antivenom is a suspension of venom neutralizing antibodies that are prepared from the serum of animals (typically horses) that are hyperimmunized against a specific venom or venoms. (Specification at p. 4, lines 19-22). Typically, animals are repeatedly injected with increasing doses of venom, and the animals' sera are collected and used to obtain antibodies that can neutralize the venom. Antivenoms are typically used to treat human snake bite victims. (*See, Id.* at p. 23, lines 1-3).

An antibody molecule is commonly referred to as an immunoglobulin ("Ig") and is shaped like a "Y." (*Id.* at 2, lines 25-27). Exposing an antibody molecule to the enzyme pepsin results in the two upper arms of this "Y" splitting from the stem of the molecule

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but remaining attached to each other. This results in one $F(ab)_2$ fragment (the two upper arms attached to each other) and an Fc fragment (the stem). (*Id.* at lines 27-31.)

Exposing an antibody molecule to the enzyme papain results in the two upper arms of this "Y" splitting both from the stem of the molecule and from each other. (*Id.* at lines 41-43). This results in two separate Fab fragments (the two upper arms) and an Fc fragment (the stem). (*Id.* at lines 27-31).[1] The desired Fab fragments can then be purified by using an affinity column that separates the Fab fragments from the Fc fragments. (*Id.* at p. 7, lines 1-14; p. 8, line 37 through p. 9, line 4; Fig. 6; Fig. 8).

VI. Issues

Whether the Examiner properly made the following rejections:

A. rejection of claims 40-42 and 45-47 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification;

B. rejection of claims 40-42 and 45-47 under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al. as evidenced by Stedman's Medical Dictionary; and

C. rejection of claims 45-47 under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al.

The Examiner also rejected claims 40-42 in the final Office Action of April 14, 1998 under 35 U.S.C. § 112, first paragraph, because the specification allegedly did not provide an adequate written description for the recitation of "antivenom" (Paper No. 33 at p. 2). Appellants responded to this rejection on several grounds in the Response

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[1] "Fab" is sometimes written "F(ab)," and $F(ab)_2$ is sometimes written "$F(ab)_2$ or Fab'_2."

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After Final of May 4, 1998. In the Advisory Action of June 24, 1998, the Examiner indicated that the Response would be entered upon filing an Appeal Brief and stated "the rejections as enunciated in the enclosed note remain for reasons of record." (Paper No. 37 at p. 1.) The "enclosed note," a complete Office Action, does not mention the previous rejection of claims 40-42 under 35 U.S.C. § 112, first paragraph, for an alleged lack of written description for the recitation of "antivenom." Since this rejection no longer remains, it is not an issue in this Appeal.

VII. Grouping of Claims

A. Claims 40-42 and 45-47 stand or fall together concerning the 35 U.S.C. § 112, first paragraph, written description rejection for purposes of this appeal only.

B. Claims 40-42 and 45-47 stand or fall together concerning the 35 U.S.C. § 103 rejection over Sullivan et al. in view of Coulter et al. and Smith et al. as evidenced by Stedman's Medical Dictionary for purposes of this appeal only.

C. Claims 45-47 stand or fall together concerning the rejection under 35 U.S.C. § 103 over Sullivan et al. in view of Coulter et al. for purposes of this appeal only.

VIII. Argument

Appellants will address each of the three grounds of rejection in the order specified by 37 C.F.R. § 1.192(c)(8).

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A. Rej ction of Claims 40-42 and 45-47 under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 40-42 and 45-47 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification. Specifically, the Examiner contends that the specification does not support the recitation of "essentially free from contaminating Fc." The Examiner repeatedly states that the specification and original claims "do not recite that the claimed Fab are essentially free from contaminating Fc" because "[t]he specification discloses that the claimed F(ab) produced an electrophoresis wherein no precipitation band against anti-Fc antibodies is seen." (Paper No. 33 at p. 3, lines 3-6, 7-10; *see also* Paper No. 37 at p. 2, lines 7-10, 12-14.) Appellants respectfully request that the Board reverse this rejection because the specification does describe Fab fragments that are essentially free from contaminating Fc, and the Examiner has applied an impermissible literal support test for written description support.

1. The Specification Indicates the Claimed Invention Can Include Immaterial Amounts of Fc Fragments

The Examiner has observed correctly that the specification discloses Fab fragments that were free from contaminating Fc. (Paper No. 33 at p. 3, lines 7-10). More specifically, the embodiment reflected in Figure 2 shows that digesting an antibody molecule with papain for 48 hours results in Fab fragments that do not precipitate a band against anti-Fc antibodies. (Specification at sentence bridging pp. 16 and 17).

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However, in another embodiment, the specification also states that when the papain is not allowed enough time to fully digest the antibody, a very small amount of Fc fragments may remain. More specifically, the specification states that digesting an antibody molecule with papain for only four hours results in fragments that produce, "a **slight hint** of a F(c) reaction." (*Id.* at 17, lines 27-28; emphasis added). This disclosure fully supports the recitation of "essentially free from contaminating Fc" in claims 40-42 and 45-47.

Since the written description requirement is directed to "a person skilled in art," 35 U.S.C. § 112, first paragraph, "the disclosure need only reasonably convey to persons skilled in the art that the inventor[s] had possession of the subject matter in question." *Fujikawa v. Wattanasin*, 39 U.S.P.Q.2d 1895, 1904 (Fed. Cir. 1996); *Ex parte Harvey*, 3 U.S.P.Q.2d 1626, 1628 (PTO Bd. Pat. App & Int'f. 1986). "How the specification accomplishes this is not material." *In re Alton*, 37 U.S.P.Q.2d 1578, 1581 (Fed. Cir. 1996) (quoting *In re Wertheim*, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976)). The specification would have conveyed to one skilled in the art that Appellants had possession of the claimed subject matter because the discussion of a "slight hint of a Fc reaction" on page 17 would have conveyed to one skilled in the art that Appellants had possession of Fab fragments "**essentially** free from contaminating Fc," as well as "free from contaminating Fc."

That the specification does not devote more discussion to this aspect of the claimed invention in no way affects the adequacy of its written description. "Certainly no length requirement exists for a disclosure to adequately describe the invention." *In*

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re Hayes Microcomputer Prods. Inc., 25 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1992). Rather, "the adequacy of the description of an invention depends on its content in relation to the particular invention, not its length." *Id.* As the specification describes, the claimed invention attempts to minimize the presence of Fc fragments, but the discussion of a "slight hint of a Fc reaction" indicates that it does not necessarily result in the total absence of Fc fragments.

The specification discusses two problems with previous antivenoms—an allergic reaction to extraneous horse proteins in the antivevom and an allergic reaction to the whole antibody. (*Id.* at p. 4, lines 35-40.) Dr. Findley E. Russell discussed this second problem (serum sickness) and its relationship to antibody fragments in his First Declaration. Soon after the development of the first antivenoms, doctors recognized that they could elicit serum sickness. (First Russell Decl. at ¶ 21.) Serum sickness occurs so often and is so dangerous that the leading commercial antivenom can only be obtained in a kit that also contains serum to test for serum sickness before administering the antivenom. (*Id.*)

In order to reduce serum sickness, Appellants produced an improved antivenom comprising Fab fragments by digesting immunoglobulins with papain and removing the Fc fragments, which are antigenic to humans. (Specification at p. 11, lines 21-26; p. 23, lines 17-21.) Specifically, Appellants took a known whole antivenom, purified its antibodies, and ran them over a column containing papain to digest the antibodies. (*Id.* at pp. 15-16.) Appellants then took the resulting solution of Fab and Fc fragments, ran

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the solution over an affinity column, and eluted off the resulting purified Fab fragments to separate the Fab fragments from the Fc fragments. (*Id.* at p. 16, lines 2-10).

Figure 2 shows the results of an immunoelectrophoresis used to detect contaminants in the resulting Fab solution obtained by digesting the known antivenom for 48 hours with papain. The immunoelectrophoresis shows no contaminating Fc fragments. (*Id.* at pp. 16-17; Fig. 2.)

Figure 4 shows the results of a second immunoelectrophoresis that differed from this first immunoelectrophoresis only in the amount of time the papain was allowed to digest the known antivenom. Unlike the 48-hour digest of Figure 2, Figure 4 involved a four-hour digest. (Specification at pp. 16-17; Fig. 4.) This four-hour papain digestion was weaker than the 48-hour digestion (specification at p. 17, line 5) in that the antibody molecules apparently were not 100% digested to Fab fragments. (*Id.* at line 28; Fig. 4.)

Given their goal of reducing serum sickness by removing Fc fragments from the Fab fragments, Appellants contemplated that papain digestions of longer than four hours might be preferred to remove all Fc fragments and obtain Fab fragments free from contaminating Fc fragments. (*Id.* at lines 34-35). However, Appellants also recognized that the slight hint of an Fc reaction seen with the four-hour digest was so small as to not be a major concern, so that their preferred digestion period included, as a lower limit, four hours. (*Id.*)

Consideration of Appellants' description of their embodiment that permits the inclusion of some Fc fragments in relation to the claimed invention reveals that it would have conveyed that Appellants' invention attempts to reduce serum sickness by

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minimizing the presence of Fc fragments, but it does not necessarily result in the total absence of Fc fragments. In relation to Appellants' goal of reducing serum sickness by minimizing the contaminating Fc fragments, their indication that their preferred papain digestion period could result in "a slight hint of an Fc reaction," would have conveyed to one skilled in the art that Appellants invented Fab fragments essentially free from contaminating Fc as determined by electrophoresis using an anti-Fc antibody and that they had invented an antivenom comprising such Fab fragments.

2. The Specification Did Not Need to Use The Claim Term "Essentially"

The Federal Circuit, the Court of Customs and Patent Appeals, the Board, and the Patent and Trademark Office, have all repeatedly rejected any requirement that the specification use the same words that the claims use. *See, e.g.*, *Alton*, 37 U.S.P.Q.2d at 158, 159 (rejecting *ipsis verbis* and explicit description requirements); *In re Herschler*, 20 U.S.P.Q. 711, 717 (C.C.P.A. 1979)(rejecting *haec verba* requirement); *Ex parte Yamaguchi*, 16 U.S.P.Q.2d 1805, 1807 (PTO Bd. Pat. App. & Int. 1988)(rejecting *ipsis verbis* requirement); M.P.E.P. § 2163.02, p. 2100-141 (7th Ed. 1998)(rejecting *haec verba* requirement). Despite the clear rejection of a literal support requirement for an adequate written description, an examination of the Examiner's language in the final Office Action shows that the Examiner rejected claims 40-42 and 45-47 on this very basis. For example, the Examiner stated:

> The specification and original claims 27 and 29 **do not recite** that the claimed F(ab) are essentially free from contaminating F(c). They **recite** that the claimed F(ab)

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> produce an electrophoresis wherein no precipitation band against anti-Fc antibodies is seen.

(Paper No. 33 at 3, lines 2-5; emphasis added). The Examiner makes the same point in the very next paragraph:

> [t]here is **no disclosure** in the specification as originally filed that the claimed F(ab) are essentially free from contaminating Fc. The specification **discloses** that the claimed F(ab) produce an electrophoresis wherein no precipitation band against anti-Fc antibodies is seen.

(Paper No. 33 at 3, lines 6-9; emphasis added).

In the Advisory Action of June 24, 1988, the Examiner again relied upon these same reasons for maintaining the rejection

> The specification and original claims 27 and 29 **do not recite** that the claimed F(ab) are essentially free from contaminating F(c). They **recite** that the claimed F(ab) produce an electrophoresis wherein no precipitation band against anti-Fc antibodies is seen.

(Paper No. 37 at 2, lines 7-10; emphasis added). Once again, the Examiner made the same point in the very next paragraph:

> [t]here is **no disclosure** in the specification as originally filed that the claimed F(ab) are essentially free from contaminating Fc. The specification **discloses** that the claimed F(ab) produce an electrophoresis wherein no precipitation band against anti-Fc antibodies is seen.

(Paper No. 37 at 2, lines 11-14; emphasis added).

By repeatedly emphasizing that the specification does not contain the specific phrase "essentially free from," the Examiner appears to have applied an improper literal support requirement. Since a literal support requirement for an adequate written

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description has been uniformly rejected, Appellants respectfully request that the Board reverse this rejection.

Although the specification does not expressly use it, the adverb "essentially" has long been recognized in patent law as including elements that "do not **materially** affect the **basic** and **novel** characteristic" of the claimed invention when nonrecited elements are otherwise excluded from a claim by a closed transitional phrase. (*See* M.P.E.P. § 2111.03 (citing *In re Hoechst*, 190 U.S.P.Q. 461, 463 (C.C.P.A. 1976); emphasis added). Thus, "essentially free from" opens claims to elements that do not materially affect the basic and novel characteristics of the claimed invention. In this case, the presence of minor amounts of contaminating Fc that do not materially affect the basic and novel characteristics of the claimed invention, such as the slight trace of the 4 hour digest, are encompassed by the claims. In other words, Fc may be present in detectable levels, but it may not be present in levels that result in serum sickness. (*See, e.g.*, specification at 11, lines 11-29).

Appellants have shown that the specification would have conveyed to one skilled in the art that they invented Fab fragments that had immaterial amounts of contaminating Fc fragments and that they invented an antivenom containing such Fab fragments. Appellants have also shown that the specification's conveyance to one skilled in the art that Appellant had invented such Fab fragments and such an antivenom support the recitation of "essentially free from" contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies. Accordingly,

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Appellants respectfully request reversal of the rejection of claims 40-42 and 45-47 under 35 U.S.C. § 112, first paragraph.

B. Rejection of Claims 40-42 and 45-47 under 35 U.S.C. § 103

The Examiner rejected claims 40-42 (the antivenom claims) and 45-47 (the Fab fragment claims) under 35 U.S.C. § 103 as allegedly being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al., as evidenced by Stedman's Medical Dictionary. Specifically, the Examiner asserted that it would have been obvious to one of ordinary skill in the art to use Sullivan et al's purified antivenom against venom of the Crotalus genus to produce antivenom compositions comprising Fab fragments using Coulter et al's method for producing Fab fragments free of Fc fragments based upon Smith et al.'s success with Fab fragments to digoxin. (Paper No. 21 at pp. 3-4.)[2] The Examiner relies upon Stedman's Medical Dictionary for the definition of "antivenom."

Sullivan *et al.* used affinity chromatography to isolate and purify whole antibody molecules from antivenom preparations. Coulter *et al.* digested whole antibody to the toxin textilotoxin with papain to form Fab fragments and found that their Fab fragments and the whole antibody molecules "were equivalent" in their ability to neutralize textilotoxin in rabbits. (Coulter *et al.* at p. 202.) Smith *et al.* digested whole antibody to the toxin digoxin to form Fab fragments and found that their Fab fragments were

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[2] The Examiner has relied upon this reasoning in all subsequent Office Actions, including the final Office Action of April 14, 1998. (*See, e.g.,* Paper No. 33 at pp. 3-4.)

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distributed and excreted more rapidly than whole antibody molecules in rabbits. (Smith *et al.* at 384.)

According to the Examiner, one of ordinary skill in the art would have been motivated to combine the Sullivan et al., Coulter et al., and Smith et al. references because Smith et al. teaches the advantages of Fab fragments over whole antibodies for the neutralization and clearance of toxic substances. (*Id.*) Appellants respectfully request that the Board reverse this rejection because the Examiner relied upon his hindsight belief that the claimed invention is obvious when the evidence shows the absence of a reasonable expectation of success at the time of Appellants' invention.

1. One Skilled in The Art Would Not Have Predicted That Results With a Single Venom Toxin (such as Coulter et al.'s) Could Be Extrapolated to Whole Venoms

Appellants will first address the Coulter *et al.* reference because the Examiner appears to have consistently misunderstood both its teachings and Appellants' evidence of the lack of an expectation of success based upon the Coulter *et al.* reference.

Coulter *et al.* used textilotoxin, the primary toxin in the venom of the Australian brown snake (*Pseudonaja textilis*). (Coulter *et al.* at p. 199, last sentence; First Russell Decl. at ¶ 46.) The pending claims recite a snake of the genus Crotalus, a genus of the family Crotalidae. As can be seen from its name, the snake Coulter *et al.* used is not a member of the genus Crotalus, nor is it even of the same family as the Crotalus genus. Rather, it is a member of the genus *Pseudonaja*. (Coulter *et al.* at 199.) Indeed, Coulter *et al.'s* snake is an elapid (Russell (1996) Toxic Effects of Animal Toxins. In

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Casarett and Doull's Toxicology: The Basic Science of Poisons, (5th Ed.) at p. 802 (attached as Exhibit 10 to the First Russell Declaration)), and the elapids are of the family Elapidae, not Crotalidae. (*Snake Venom Poisoning* at p. 5.)

Furthermore, while it might now appear to the Examiner, after having read Appellants' disclosure, to be obvious to combine Coulter *et al.'s* teaching concerning Fab fragments with Sullivan *et al.'s* antivenom, "hindsight is not a justifiable basis on which to find" that an invention was obvious. *Amgen v. Chugai Pharm. Co. Ltd.*, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Rather, the prior art, not Appellants' disclosure, must have provided a reasonable expectation of success. *Id.* at 1022; *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). This rejection, however, depends upon a hindsight-aided application of the teachings from Appellants' disclosure, not the prior art. The evidence Appellants have submitted shows that this rejection fails for a lack of the required expectation of success.

Textilotoxin is simply **a single toxin** from Australian brown snake venom. Although venoms can be simple substances, as in some marine animals, in snakes they are often very complicated mixtures of many individual toxins. (First Russell Decl. at. ¶ 15, ¶ 47; Smith Decl. at ¶ 6.) In some venoms of Crotalus snakes, there may be 100 different protein fractions. (First Russell Decl. at ¶ 15.) Due to their complexity, the full composition of snake venoms is unknown. (*Id.*) Not only is the composition of snake venoms complicated and their exact composition unknown, but the pharmacological effects of some constituent toxins are unknown. (*Id.* at ¶ 16.)

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Due to the unknown composition of snake venoms and the unknown effect of even the identified toxins in snake venoms, basic toxicology texts caution against extrapolating results from individual venom toxins (like Coulter *et al.'s*) to whole venoms (like the claims recite). (*Toxic Effects of Animal Toxins* at p. 802; *Snake Venom Poisoning* at p. 168.) Accordingly, the Examiner is incorrect in attempting to extrapolate Coulter *et al.'s* results with Fab fragments to a single snake venom toxin to the results that would have been expected with Fab fragments to an entire snake venom comprising many unknown toxins of unknown effect. As Dr. Russell stated, "one would not have expected Coulter *et al.'s* results with Fab to a single **toxin** to predict similar results with Fab to a Crotalidae snake **venom**, including a Crotalus snake **venom**." (First Russell Decl. at ¶ 47; emphasis in original.)

Since Coulter *et al.* used Fab fragments to a toxin from the venom of a snake of a different genus than the claims recite, and since one of ordinary skill in the art would not have expected results with Fab fragments to a single venom toxin to predict what would occur with Fab fragments to an entire Crotalus venom, any rejection relying upon the Coulter *et al.* reference must fail. Not only was there no reasonable expectation of success based upon the Coulter et al. reference before Appellants' invention, there was no reasonable expectation of success in using Fab antivenom fragments based upon <u>any</u> references, including Sullivan et al., Coulter et al., and Smith et al.

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2. Befor App llants' Inv nti n, Fab Fragments W r Expected to B In ff ctiv

Appellants submitted numerous references and the Declarations of Dr. Damon Smith, Dr. John B. Sullivan, and Findley E. Russell, M.D., Ph.D., which prove that, while the claimed invention might now appear to the Examiner, in hindsight, to be obvious, at the time of Appellants' invention, the claimed invention would not have been obvious because one of ordinary skill in the art would not have had a reasonable expectation of success. Indeed, Dr. Sullivan "and others questioned whether anti-venom F(ab)'s would be effective [antivenoms]" (Sullivan Decl. at ¶ 9), and Dr. Sullivan and others actually believed that Fab fragments would "fail or **increase** toxicity of the venom." (Sullivan Decl. at ¶ 13; emphasis in original.)

The only commercially available antivenom at the time of Appellants' invention for North American snakes of the Crotalus genus was Antivenin [Crotalidae] Polyvalent (equine origin) ("ACP"), which first became available in 1947. (First Russell Decl. at ¶ 20; Smith Decl. at ¶ 7.) This antivenom suffers the serious problem suffered by other antivenoms of often causing serum sickness, an allergic reaction to the antivenom that is sometimes as deleterious as the venom. (First Russell Decl. at ¶ 20; specification at p. 4, lines 35-40.) Over 75% of envenomation patients who receive ACP suffer from serum sickness. (First Russell Decl. at ¶ 20.) This danger can be so great that physicians may not administer this antivenom for some cases of envenomation, and ACP can only be obtained in a kit that also contains test serum for possibly detecting serum sickness. (*Id.*)

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Because of the serious problem of serum sickness, extensive research had been performed on developing better antivenoms. (First Russell Decl. at ¶ 24.) As Appellants discussed above, it was generally believed that "given possession of the antibody active site, the smaller the antibody molecule, the better. (Specification at p. 3, lines 1-2.) Thus, much of this research focused on immunoglobulin fragments, which may not provoke an immune reaction. (First Russell Decl. at ¶ 24.) In the late 1960's, researchers began experimenting with antivenoms comprising $F(ab)_2$ fragments, and such antivenoms first became commercially available in 1969. (*Id.*; Smith Decl. at ¶ 7.) Although the smaller size of the $F(ab)_2$ fragments results in less serum sickness, such antivenoms appear less effective than antivenoms comprising whole immunoglobulin. (First Russell Decl. at ¶ 25.) Consequently, Crotalidae antivenoms comprising $F(ab)_2$ fragments were not produced in the United States. (First Russell Decl. at ¶ 24).

Although serum sickness had long been recognized as a major problem with antivenoms, and although smaller antibody fragments had long been known to be less immunogenic, no researcher developed antivenoms comprising the smaller Fab fragments prior to Appellants' invention. (*Id.* at ¶ 25; Sullivan Decl. at ¶ 5.) Indeed, there had been no significant improvements in commercial antivenoms since 1969, when an $F(ab)_2$ antivenom was commercially sold. (Smith Decl. at ¶ 7.) Development of antivenoms comprising antibody fragments halted at the larger $F(ab)_2$ fragments because the larger $F(ab)_2$ fragments appeared to some of ordinary skill in the art to be less effective than whole antibody. (First Russell Decl. at ¶ 25.)

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Not only did the $F(ab)_2$ fragments, which are larger than Fab fragments, appear to be less effective than whole antibody molecules, but those of ordinary skill in the art expected Fab fragments to be even less effective than the disappointing $F(ab)_2$ fragments for several reasons. (First Russell Decl. at ¶ 26; Sullivan Decl. at ¶ 5; Smith Decl. at ¶ 9.) First, Fab fragments cannot stearically hinder the binding of a venom protein to its tissue target as well as $F(ab)_2$ fragments because Fab fragments have only one active site. (First Russell Decl. at ¶ 29; Sullivan Decl. at ¶ 8.) The two binding sites on $F(ab)_2$ fragments allow them to bind to repeating antigenic determinants on a venom antigen, and this repetitive determinant binding stearically hinders the venom antigen from binding to its active site.

Second, since $F(ab)_2$ fragments contain two antigen binding sites, each individual $F(ab)_2$ fragment can bind two antigens. (Steward Sell, *Basic Immunology: Immune Mechanisms in Health and Disease*, at p. 89, Fig. 6-3 (1987).) As more $F(ab)_2$ fragments cross-link more antigens, they form larger complexes which, eventually, become large enough that they precipitate from solution. *Id.* In contrast, since Fab fragments have only one antigen binding site, they cannot form cross-linked complexes and precipitate the antigens. (Smith Decl. at ¶ 9.)

Third, those of ordinary skill in the art expected that Fab fragments would not be effective because they would be cleared before the venom. Many venom toxins are large, hydrophobic molecules, and they are usually injected deep into subcutaneous tissues. (First Russell Decl. at ¶ 30; Smith Decl. at ¶ 8.) These individual toxins are released slowly from the injection site, resulting in the "venom depot effect" whereby the venom toxins continue to be released into the circulatory system long after the initial

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bite. (First Russell Decl. at ¶ 30; Smith Decl. at ¶ 8.) Venom protein continues to be released from the injection site for weeks (Sullivan Decl. at ¶ 5(a)), and has been detected in a patient 46 days after envenomation. (Owenby et al., *Southern Medical Journal* (1990).)

Fab fragments have a molecular weight of around 45-55 Kd. (First Russell Decl. at ¶ 31.) This relatively small size allows the renal system to remove Fab fragments, resulting in a half-life of about 17 hours. (*Id.*) Indeed, the renal system completely eliminates Fab fragments in only 24-26 hours. (*Id.*)

$F(ab)_2$ fragments, in contrast, are about twice as large as Fab fragments–too large for the renal system to remove them. (*Id.* at ¶ 32.) Thus, they have a much longer half-life than Fab fragments, approximately 50 hours versus approximately 17 hours. (*Id.*) Given the renal system's rapid removal of Fab fragments, especially compared to $F(ab)_2$ fragments, and the venom depot effect, those of ordinary skill in the art expected that there would be no remaining Fab fragments to neutralize later-released venom toxins. (*Id.* at ¶ 32; Smith Decl. at ¶ 8.)

3. Before Appellants' Invention, Fab Fragments Were Actually Expected to Be Harmful

Not only did those of ordinary in the skill in the art believe that Fab fragments would be ineffective before Appellants' invention, they actually expected that such an antivenom could increase the lethality of the snake venom by redistributing and concentrating its toxins. (Russell Decl. at ¶ 33; Sullivan Decl. at ¶ 13.) The binding of

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Fab fragments and venom toxins is a dynamic process, having an equilibrium where individual venom toxins are constantly bound and released. (First Russell Decl. at ¶ 34.) The renal system's rapid removal of Fab fragments, however, continually decreases the number of Fab fragments remaining to bind the venom toxins. (Smith Decl. at ¶ 8.) Those of ordinary skill in the art were concerned that Fab fragments would bind venom toxins that were released into the circulatory system and then release the venom toxins at another site, perhaps concentrating the venom toxins in areas of high blood flow like the kidneys, heart, nervous system, and lungs. (First Russell Decl. at ¶ 36; Sullivan Decl. at ¶ 5(b).) As Dr. Sullivan stated,

> I and others maintained and discussed our concerns that F(ab) [fragments] would redistribute toxic venom proteins throughout the body, thus producing venom pathology at tissue sites and organ systems not typically seen in patients treated with [whole antibodies] or $F(ab)_2$.

(Sullivan Decl. at ¶ 7.) While the toxins might have caused swelling and local necrosis at the site of envenomation, the predicted redistribution and concentration of venom toxins might result in "coagulopathy, direct cardiotoxicity, liver and kidney damage, potential central nervous system, and peripheral nervous system damage." (*Id.*) Thus, what had been a systemic toxicity with venom toxins being released slowly into the circulation could become a localized toxicity with venom toxins being concentrated in the kidneys, heart, nervous system, and lungs by this "taxi" effect. (First Russell Decl. at ¶ 36; Sullivan Decl. at ¶ 5(a).)

This taxi effect was predicted, and it was a reason why those of ordinary skill in the art did not progress beyond the known $F(ab)_2$ fragments to the smaller Fab fragments. (Sullivan Decl. at ¶ 7.) According to Dr. Sullivan, the use of Fab fragments

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to treat envenomation would have been "medically unsound and contraindicated." (*Id.* at ¶ 13.) The belief of those of ordinary skill in the art that Fab fragments would actually increase the lethality of snake venom by concentrating high molecular weight snake toxins in areas of high blood flow was not a merely theoretical concern, as Faulstich *et al.* later demonstrated.

Faulstich *et al.* (Strongly Enhanced Toxicity of the Mushroom Toxin α-Amanitin by an Amatoxin-Specific Fab or Monoclonal Antibody. 26 *Toxicon* 491 (1988) (copy attached as Exhibit 7 to first Russell Declaration)) conducted a series of studies attempting to treat α-amatoxin poisoning with Fab fragments. Alpha-amatoxin is a high molecular weight toxin that is similar to some snake venom toxins. (First Russell Decl. at ¶ 37.) As a high molecular weight toxin, α-amatoxin cannot be cleared by the renal system. (*Id.*) Rather, like many snake toxins, it is cleared by the liver. (*Id.*) Since α-amatoxin is concentrated in the liver after oral ingestion, it is primarily toxic to liver cells. (*Id.*)

Faulstich *et al.* discovered that the Fab fragments did not decrease the toxicity of α-amatoxin in mice, but rather increased the toxicity of α-amatoxin by a factor of 50. (*Faulstich et al.* at p. 497.) Furthermore, the Fab fragments resulted in α-amatoxin being specifically toxic to kidney cells rather than liver cells. (*Id.*) This is exactly what one of ordinary skill in the art would have predicted. (First Russell Decl. at ¶ 38.) The Fab fragments bound the high molecular weight α-amatoxin, and then unbound it in their state of equilibrium at sites of high blood flow. (*Id.*) This unbinding at sites of high blood flow, especially the kidneys, resulted in the α-amatoxin being concentrated in

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these tissues and killing them. (*Id.*) Thus, Fab fragments greatly increased the toxicity of this high molecular weight toxin by concentrating it in areas of high blood flow.

Faulstich *et al's* results with Fab fragment directed to a high molecular weight toxin stood in contrast to Balthazar *et al.'s* results with Fab fragments to the low molecular weight toxin digoxin. (Balthazar *et al.* (1994) Utilization of Antidrug Antibody Fragments for the Optimization of Intraperitoneal Drug Therapy: Studies Using Digoxin as a Model Drug. *J. Pharm. Exp. Ther.* 268, 734 (attached at Exhibit 8 to the First Russell Declaration).) Digoxin is unlike most Crotalidae venom toxins; it is a very small molecule; small enough that the renal system can clear the Fab-digoxin complex. (First Russell Decl. at ¶ 39; Smith Decl. at ¶¶ 8, 10.) Since the renal system can filter the Fab-digoxin complex, the Fab fragments did not redistribute and concentrate digoxin, as one of ordinary skill in the art would have predicted. (First Russell Decl. at ¶ 39.) Accordingly, Balthazar *et al.* found that F(ab) fragments effectively treated digoxin toxicity, just as Smith *et al.*, upon which the Examiner relies, found.

However, Balthazar *et al.* recognized the potential problems of Fab therapy for large toxins, like α-amatoxin and some Crotalidae venom toxins:

> First, the alteration of drug distribution which accompanies antibody drug complexation may result in a **potentiation of drug toxicities** or the development of **new drug toxicities in certain cases** . . . . The risk of **redistributing systemic toxicity**, rather than minimizing systemic toxicity, should be appreciated as a potential outcome of the proposed approach.

(Balthazar *et al.* at p. 738, cols. 1-2; emphasis added.)

Accordingly, those of ordinary skill in the art were concerned that treatment with an antivenom comprising Fab fragments would actually be harmful for the treatment of

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high molecular weight venom toxins because the Fab fragments would redistribute high molecular weight toxins to areas of high blood flow, creating new toxicities. Faulstich *et al.* confirmed this concern with a toxin that is of a similar molecular weight as many snake venom toxins. (First Russell Decl. at ¶ 41.) Balthazar *et al.* reinforced this concern by showing that this effect did not occur with a low molecular weight toxin that the renal system could clear as part of an Fab-toxin complex. (First Russell Decl. at ¶ 42.) Indeed, despite the effectiveness of their treatment, Balthazar *et al.* specifically discussed their concern that Fab fragments might alter drug toxicities or redistribute systemic toxicities.

These *in vivo* mechanisms that led those of ordinary skill in the art to expect that the claimed invention would not be effective show that the Examiner's reliance upon the Coulter *et al.* reference for teaching that Fab fragments have a higher sensitivity than whole antibody in *in vitro* tests is misplaced. Coulter *et al.* did not treat envenomation with their Fab fragments. Rather, Coulter *et al.* first mixed textilotoxin with their Fab fragments *in vitro*. (Coulter *et al.* at p. 201, 3rd full paragraph.) Coulter *et al.* then injected the already bound Fab-textilotoxin complex intravenously. This treatment with Fab fragments resulted in neutralization that was essentially equivalent to the treatment with the IgG fragments, just as one of ordinary skill in the art would have expected. (First Russell Decl. at ¶ 48.) Since the Fab-textilotoxin mixture was first mixed *in vitro* and then injected intravenously, the Fab did not have the opportunity to redistribute and concentrate the textilotoxin in high blood flow parts. (*Id.*) Accordingly, the Coulter *et al.* reference would not have provided a reasonable expectation of success for an

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antivenom comprising Fab fragments to any venom toxins, despite the Examiner's assertion to the contrary. (*Id.*)

Once again, this was not a merely theoretical concern, as Sorkine *et al.* later demonstrated. Sorkine *et al.* conducted a similar experiment in 1983 by mixing Fab fragments with a snake venom before injecting the mixture into a mouse, and they obtained similar results. (Sorkine *et al.* (1995) Comparison of $F(ab')_2$ and Fab Efficiency on Plasma Extravasation Induced *Viper aspis* Venom. *Toxicon* 33, 257 (attached as Exhibit 11 to the First Russell Declaration).) This treatment resulted in a considerable reduction in capillary permeability. However, the Fab fragments were much less effective when they were administered *in vivo* separately from the venom. As Sorkine *et al.* state "these data showed firstly that the *in vitro* neutralization of the venom by immunoglobulin fragments does not reflect their *in vivo* efficiency." (Sorkine *et al.* at 257.) Thus, the Sorkine *et al.* reference shows that one would not have expected Coulter *et al.*'s *in vitro* neutralization results to predict the effectiveness of antivenoms comprising Fab fragments *in vivo*. (First Russell Decl. at ¶ 50.)

In sum, prior to Appellants' invention, those of ordinary skill in the art did not have a reasonable expectation of success that an antivenom comprising Fab fragments to Crotalidae venom would be effective. Obviousness requires that "[b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not [Appellants'] disclosure," *Vaeck*, 20 U.S.P.Q.2d at 1442, and Appellants have shown that that is not the case here. Despite the known problems with the commercially available venom for Crotalidae envenomation since 1947, and the well-

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known fact that smaller immunoglobulin fragments are less immunogenic, those of ordinary skill in the art had not progressed beyond antivenoms comprising the disappointing $F(ab)_2$ fragments to the smaller Fab fragments because they expected Fab fragments to be not just ineffective, but actually more harmful to the patient that no treatment at all. For these reasons, Appellants respectfully request that the Board reverse the rejections of claims 40-42 and 45-47 under 35 U.S.C. § 103.

C. Rejection of Claims 45-47 Under 35 U.S.C. § 103

The Examiner rejected claims 45-47 (the Fab fragment claims) under 35 U.S.C. § 103 as allegedly being unpatentable over Sullivan *et al.* in view of Coulter *et al.* Specifically, the Examiner asserted that Sullivan *et al.* teach an antivenom comprising whole antibody against venom of a snake of the Crotalus genus and that Coulter *et al.* teach that Fab fragments that are free from contaminating Fc fragments are more sensitive than whole antibody when used in an *in vitro* assay. (Paper No. 31 at pp. 8-9.) Appellants respectfully request that the Board reverse this rejection because the Examiner again improperly relied upon his hindsight belief that the claimed invention is obvious, when the evidence shows the absence of a reasonable expectation of success at the time of Appellants' invention.

Again, "hindsight is not a justifiable basis on which to find" that an invention was obvious. *Amgen,* 18 U.S.P.Q.2d at 1023. Rather, at the time of the invention, there must have been a reasonable expectation of success, and that expectation must come from the prior art, not Appellants' disclosure. *Id.* at 1022.

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Appellants showed above that the combination of Sullivan et al., Coulter et al., and Smith et al. does not render claims 45-47 (the Fab fragment claims), as well as claims 40-42 (the antivenom claims), obvious because there would not have been a reasonable expectation of success. Since the combination of these three references does not render claims 45-47 obvious, the combination of only Sullivan et al. and Coulter et al. cannot render claims 45-47 obvious.

While it might now appear to be obvious to combine Coulter *et al.'s* teaching concerning Fab fragments with Sullivan *et al.'s* antivenom, "hindsight is not a justifiable basis on which to find" that an invention was obvious. *Amgen,* 18 U.S.P.Q.2d at 1023. Rather, the prior art, not Appellants' disclosure, must have provided a reasonable expectation of success. *Id.* at 1022; *Vaeck*, 20 U.S.P.Q.2d at 1442. This rejection, however, also depends upon a hindsight-aided application of the teachings from Appellants' disclosure, not the prior art. The evidence Appellants have submitted shows that this rejection lacks the required expectation of success.

As Appellants showed above, Coulter et al used a venom toxin from a snake of a genus *(Pseudonaja)* different from the genus the pending claims recite (*Crotalus*). More importantly, Coulter *et al.* used a single venom toxin, not an entire venom, and basic toxicology texts caution against extrapolating from results with single venom toxins (like Coulter et al's) to whole venoms (like the claims recite). (*Toxic Effects of Animal Toxins* at p. 802; *Snake Venom Poisoning* at p. 168.) Thus, one of ordinary skill in the art "would not have expected Coulter *et al's* results with Fab to a single **toxin** to predict similar results with Fab to a Crotalidae snake **venom**; including a Crotalus

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snake **venom** (First Russell Decl. at ¶ 47; emphasis in original), as the Examiner has alleged.

Sullivan cannot remedy the deficiencies of Coulter et al. Even the Examiner has not suggested that Sullivan et al. contains any teaching or suggestion concerning Fab fragments. Since the evidence shows that, before Appellants' invention, there would not have been a reasonable expectation of success, Appellants respectfully request that the Board also reverse the rejection of claims 45-47 under 35 U.S.C. § 103.

IX. CONCLUSION

In view of the forgoing reasons, Appellants respectfully request that the rejection of the pending claims under 35 U.S.C. § 112, first paragraph, and the two rejections of the pending claims under 35 U.S.C. § 103 be reversed.

If further extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such an extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 that are not enclosed herewith, including any

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fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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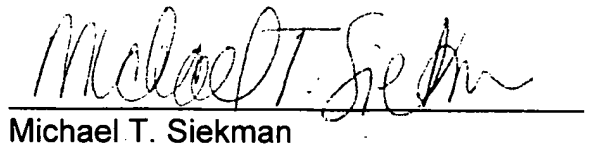
By: 

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APPENDIX I

40. An antivenom composition comprising Fab fragments which bind specifically to a venom of a snake of the Crotalus genus and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically acceptable carrier.

41. The antivenom composition of claim 40, wherein an antibody source for said Fab fragments is IgG(T).

42. The antivenom composition of claim 40, wherein an antibody source for said Fab fragments is polyvalent IgG(T).

45. Fab fragments which bind specifically to a venom of a snake of the Crotalus genus, and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using an anti-Fc antibody.

46. The Fab fragments of claim 45, wherein an antibody source for said Fab fragments is IgG(T).

47. The Fab fragments of claim 45, wherein an antibody source for said Fab fragments is polyvalent IgG(T).

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